SECTION ON MICROBIOLOGY

FEBRUARY 16, 1949

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Alphonse R. Dochez

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Columbia University

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Yale Kneeland (by invitation)

College of Physicians and Surgeons

Columbia University

GREGORY SHWARTZMAN
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HARRY MOST
Secretary
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Introduction to Studies on the Common Cold

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If we examine ancient accounts of disease we easily discover the description of a group of respiratory symptoms that exactly represents the clinical manifestations of what today we call the common cold. That it is an ancient disease and that it has continuously maintained its characteristic picture there can be very little doubt. The cold seems to be firmly established as a human disease whose character and high incidence have remained unaltered throughout the centuries. Its causative agent must therefore be, in the terms of Theobald Smith, a most efficient parasite.

For many years curiosity concerning the causation of the cold has remained active and has, especially during the period of modern bacteriology, stimulated the research activity of numerous investigators. With the development and improvement of bacteriologic techniques study of the throat and nasal flora of individuals suffering from the common cold has been the subject of repeated investigations. A number of well-characterized microörganisms have been described as being associated with certain outbreaks of the disease or with individual attacks. In general these organisms comprise Gram-positive cocci, Gram-negative cocci, such as Micrococcus catarrhalis, diphtheroid bacilli and a number of others. A specific causative relationship of these organisms to the disease has been difficult to establish convincingly because of their presence, without the production of symptoms, more or less continuously or for varying periods of time in the respiratory flora of healthy individuals.

In order to evaluate the pathogenic importance of the organisms mentioned above my colleagues and myself have studied a number of human subjects during healthy periods in order to gain complete familiarity with their nasopharyngeal flora. Later when any one of these individuals contracted a cold very careful bacteriological observations were made in order to ascertain if there appeared for the first time or in significantly increased numbers any easily recognizable organism to which a causative role might be assigned.

The results of these studies led us to certain conclusions. In the early days of the cold no new organisms appeared in the throat flora nor was there any significant increase in such potential pathogens as were already present. In fact, there generally appeared a diminution in the total number of organisms present, due in all probability to dilution by the increased amount of secretion. Whenever there was evidence of increased activity this usually occurred late and was frequently associated with some complication which had developed. Our observations led us to conclude that the common pathogens of the nasopharynx, in general, are not the initiating agents of infection of the respiratory tract of the type of common cold and that they act principally as secondary invaders of an inflammatory process causatively induced by a primary agent of unknown character.

With increasing knowledge of the pathogenic importance in infectious diseases of filterable viruses research turned toward the investigation of the possible relationship of such microörganisms to the common cold. Early important studies were those of Kruse[1] in 1914, Foster[2] in 1916, and Olitsky and McCartney[3] in 1923.

Kruse realizing the inadequacy of the evidence for a bacterial etiology studied the possibility of virus causation. He performed two experiments on students in which he inoculated the subjects intranasally with bacteria-free filtrates of nasopharyngeal washings from individuals with typical acute colds. In the first experiment positive results were obtained in four out of five volunteers. The incubation period was from 1-3 days. In the second experiment fifteen of thirty-six were positive in from 1-4 days. The incidence of spontaneous colds at the time was very low.

Foster in 1916 performed a similar set of experiments. Seven out of ten soldier volunteers were positive with one possible contact infection. Foster then attempted to cultivate the virus in Smith-Noguchi medium. Two strains were cultivated. The cultures showed a haze spreading from the area of the tissue. Small globoid bodies could be stained which appeared motile. Eleven volunteers were inoculated with the culture material and all manifested typical symptoms and characteristic appearance in the throat. Cultures from the subjects were positive for the growth of globoid bodies. Colonies were demonstrated in agar ascitic fluid. From what we know today the globoid bodies observed may have been due to small filterable Gram-negative bacteria which are constantly present in the normal throat. Some of these organisms are motile. It is possible that a true filterable virus was also present, which would account for the reproduction of the common cold in individuals inoculated with culture material.

Later studies[4] confirmed the transfer of colds from human to human by means of bacteria-free filtrates of throat washings obtained from individuals with colds. In at least one instance this infection was transferred from individual to individual in series.

In 1926 my colleagues and myself investigated the possible virus etiology of the common cold. Having learned from Dr. Francis G. Blake that chimpanzees were subject to colds resembling in every particular the human cold these animals were chosen as experimental animals. After establishing a careful quarantine, inoculation of bacteria-free material obtained from examples of typical human colds was performed. In a large percentage of instances the chimpanzees came down with colds similar in every respect to their own spontaneous colds and to the same infection in human beings. The cold could be passed from chimpanzee to chimpanzee using the established technique, and infection of healthy cage contacts also occurred. The incubation period of the disease was from 24-48 hours.

In view of the mild character of the experimental disease in animals, a similar study was made using human volunteers as subjects. The results obtained were essentially the same as those obtained with chimpanzees. The infection could also be transferred from human to human in series. The virus etiology of the common cold was thus established.

The next procedure was an attempt to cultivate the virus *in vitro*. Chick embryo medium was first used and the experiment proved successful. Large numbers of human beings were successfully infected with the tissue culture material and in one instance the culture remained infective for at least eighty transfers. Later the embryonated hen's egg was used for purposes of cultivation and successful experimental inoculations resulted. The number of egg transfers was relatively small, in one instance three and in another a few more.

No determinable changes could be observed in the medium in which the virus grew. All attempts to establish the culture virus in laboratory animals were failures. No significant tests for the presence of the virus in the culture medium could be developed either *in vitro* or *in vivo*. The virus was studied in many ways but no progress beyond animal and human inoculation took place.

The practical objective of this work was the development of a useful form of prophylactic inoculation. A number of individuals were injected with a living virus vaccine but successful immunization did not result. A number of facts militate against the success of such an undertaking, the lack of an enduring immunity following a spontaneous attack of the common cold and the absence of knowledge concerning the number of immunologic varieties of the virus of the common cold. Before further progress can be made there must be further development of the techniques for the study of the common cold virus and a great deal must be learned concerning the natural infection in man, particularly in respect to increased resistance to infection, if indeed such exists.

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Research on the Common Cold

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It has been 34 years since Kruse[1] reported that he had produced the common cold in human volunteers by inoculation of filtered nasal secretions from an assistant with a cold.

In the last 25 years great progress has been made in studies on viruses but up until the last 2 or 3 years there has been relatively little advance in our knowledge of the agent or agents of the common cold.

Kruse produced colds in 33 per cent of his first group of volunteers, the majority within 1 to 3 days after inoculation with a Berkfield filtrate of nasal washings. He was able to produce symptoms of common cold in 42 per cent of another group studied later, again the majority showing an incubation period of 1 to 3 days.